

A case report: intracoronary acetylcholine testing without a pacemaker may be one option in the left coronary artery

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Background

The intracoronary acetylcholine (ACh) and ergonovine (ER) test is employed as a pharmacological spasm provocation test. ACh causes vasoconstriction in patients with coronary endothelial dysfunction such as coronary atherosclerosis, while ER induces coronary vasoconstriction through the activation of coronary smooth muscle.

Case summary

An 84-year-old Japanese man was admitted to our hospital due to resting angina and syncope. Computed tomography coronary angiography (CTCAG) revealed severe proximal left anterior descending (LAD) coronary artery stenosis, but hybrid images of CTCAG and thallium-adenosine myocardial scintigraphy revealed no ischaemia. During syncope, inverted T waves on V5, V6 leads were recognized. After coronary arteriography, mild atherosclerotic stenosis (50%) was found at the proximal LAD artery, and we administered intracoronary ER 104 µg and 80 µg into the left and right coronary arteries because of suspected coronary spasm. However, no provoked spasm was obtained in either vessel. We administered 20, 50, and 100 µg intracoronary ACh into the left coronary artery (LCA) for 30 s without a pacemaker, because neither bradycardia nor cardiac arrest has occurred. Diffuse distal spasm was provoked after the administration of 100 µg ACh and the patient complained of typical chest pain and prodrome before syncope. The patient was diagnosed with coronary spastic angina by the ACh test but not the ER test.

Discussion

Different coronary responses between ACh and ER were observed in this case. Intracoronary ACh testing without a pacemaker may be one option in the LCA if no bradycardia or arrest occurs.

Keywords

Coronary spastic angina • Acetylcholine • Ergonovine • Pacemaker • Left coronary artery • Case report

Learning points

- Intracoronary acetylcholine testing without a pacemaker may be one option in the left coronary artery if neither bradycardia nor cardiac arrest is found.
- We could diagnose this patient as coronary spastic angina by the acetylcholine test but not the ergonovine (ER) test.
- Acetylcholine causes vasoconstriction in patients with coronary endothelial dysfunction, while ER induces coronary vasoconstriction through the activation of coronary smooth muscle. Different medicines may have the potential to document different coronary responses in even the same patients.

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Introduction

The European Society of Cardiology (ESC) guidelines and the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines classify spasm provocation testing as Class IIa and Class IIb, respectively.^{1,2} In contrast, ergonovine (ER) and acetylcholine (ACh) testing is classified as class I according to the Coronary Vasomotion Disorders International Study Group (COVADIS) report and the Japanese Circulation Society (JCS) guideline for coronary spastic angina (CSA).^{3,4} However, ACh causes vasoconstriction in patients with coronary endothelial dysfunction such as coronary atherosclerosis, while ER induces coronary vasoconstriction by way of the activation of coronary smooth muscle. Different medicines may have the potential to document different coronary responses, even in the same patients. We reported the differences in coronary responses between the two pharmacological agents.^{5,6} The majority of institutions employ one pharmacological agent, such as just ACh or ER alone, as a spasm provocation agent in each hospital.^{7,8} Fewer institutions may employ dual agents as a spasm provocation test. Furthermore, temporary pacemaker insertion is necessary for ACh tests according to the JCS guideline.⁴

In this case report, we showed the clinical benefit of the ACh test compared to the ER test, and we also demonstrated an optional ACh test without a pacemaker in the left coronary artery (LCA) after no provoked spasm by ER testing if no bradycardia has occurred.

Timeline

2 months prior to admission	Patient complained chest pain at rest and had episodes of syncope.
1 week prior to admission	Before computed tomography coronary angiography (CTCAG), he complained aura before syncope. Inverted T waves on V5, V6 leads were observed.
1 week prior to admission	CTCAG disclosed severe stenosis at the proximal left anterior descending (LAD) artery.
Day 0 (admission)	Patient admitted to our hospital for further examinations.
Day 0 (admission)	Thallium adenosine myocardial scintigraphy revealed no ischaemia in the LAD coronary artery territory.
Day 1 (admission)	Mild organic stenosis (50%) was found at the proximal LAD artery after coronary arteriography.
Day 1 (admission)	Intracoronary ergonovine test disclosed no spasm on both coronary arteries.
Day 1 (admission)	Typical diffuse spasm at the distal LAD artery was found after the administration of intracoronary 100 µg acetylcholine into the left coronary artery without a pacemaker accompanied with typical chest pain and prodrome before syncope.

Continued

Day 1 (admission)	Patient was finally diagnosed with coronary vasospastic angina.
Day 2 (admission)	Patient was medically managed with calcium channel blocker (4 mg benidipine) and nicorandil (10 mg), and patient was discharged.
6 months after discharge	Patient remained well on medical management including calcium channel blocker and nicorandil. Patients had never complained of chest pain or syncope for more than 6 months.

Case presentation

An 84-year-old Japanese male patient with chest pain at rest and syncope 2 months ago who was admitted to the hospital for further evaluation. He had a history of smoking more than 50 years but quit smoking 5 years ago. Rosuvastatin calcium 2.5 mg was administered at a neighbourhood hospital due to dyslipidaemia. His blood pressure was 121/50 mmHg, and his pulse rate was 68/min. There were no abnormal findings regarding auscultation and physical examinations. After routine electrocardiogram and cardiac ultrasonography examinations, we performed computed tomography coronary angiography (CTCAG). After an hour-long administration of 20 mg metoprolol and 5 mg nitroglycerine tape before examination by CTCAG, he complained of typical chest pain and prodrome before syncope. During the attack, bradycardia and inverted T waves in the V5, V6 leads were observed, as shown in [Figure 1B](#). We did not measure the Troponin because his chest pain disappeared within a few minutes. CTCAG revealed severe stenosis (70% <) at the proximal left anterior descending (LAD) artery according to the coronary artery disease reporting and data system (CAD-RADS),⁹ as shown in [Figure 2A, d/d](#). Hybrid images of CTCAG and thallium-adenosine myocardial scintigraphy revealed no ischaemia in the LAD coronary artery territory, as shown in [Figure 2B, e/f](#). We performed coronary angiography. However, LAD artery has a 50% stenosis. We did not measure coronary fractional flow reserve because LAD artery has just 31% stenosis by the analysis of Quantitative Coronary Angiography ([Supplementary material online, File S1](#)). We administered intracoronary injection of 64 µg ER into the LCA, but no provoked spasm was observed, as shown in [Figure 3A](#). Although we added another 40 µg ER into the LCA, no provoked spasm was recognized ([Figure 3B](#) and [Video 1A](#)). After the administration of 80 µg ER into the right coronary artery (RCA), no provoked spasm was found. We administered 20/50/100 µg intracoronary ACh into the LCA without a pacemaker for 30 s. Neither bradycardia nor cardiac arrest has occurred during or after the administration of ACh. As shown in [Figure 3C](#) and [Video 1B](#), intracoronary administration of 100 µg ACh into the LCA disclosed diffuse spasm at the distal LAD artery accompanied by usual chest pain and slight ST elevation (0.5 mm) on V2–V4 anterior leads. After the administration of nitroglycerine, no stenosis was observed in the distal LAD artery ([Figure 3D](#) and [Video 1C](#)). We diagnosed the patient with CSA. A calcium channel antagonist (4 mg benidipine) and nicorandil (10 mg) were started. Since then, the patient has never complained of chest pain or syncope for more than 6 months.

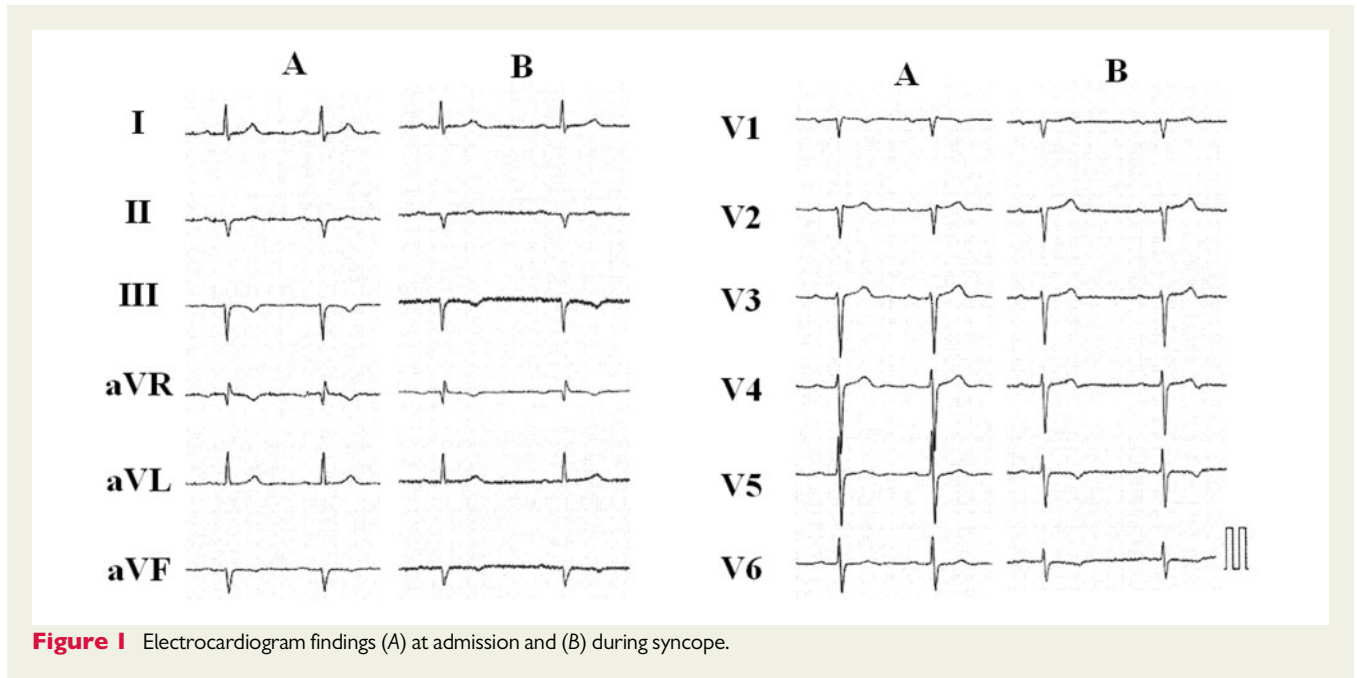


Figure 1 Electrocardiogram findings (A) at admission and (B) during syncope.

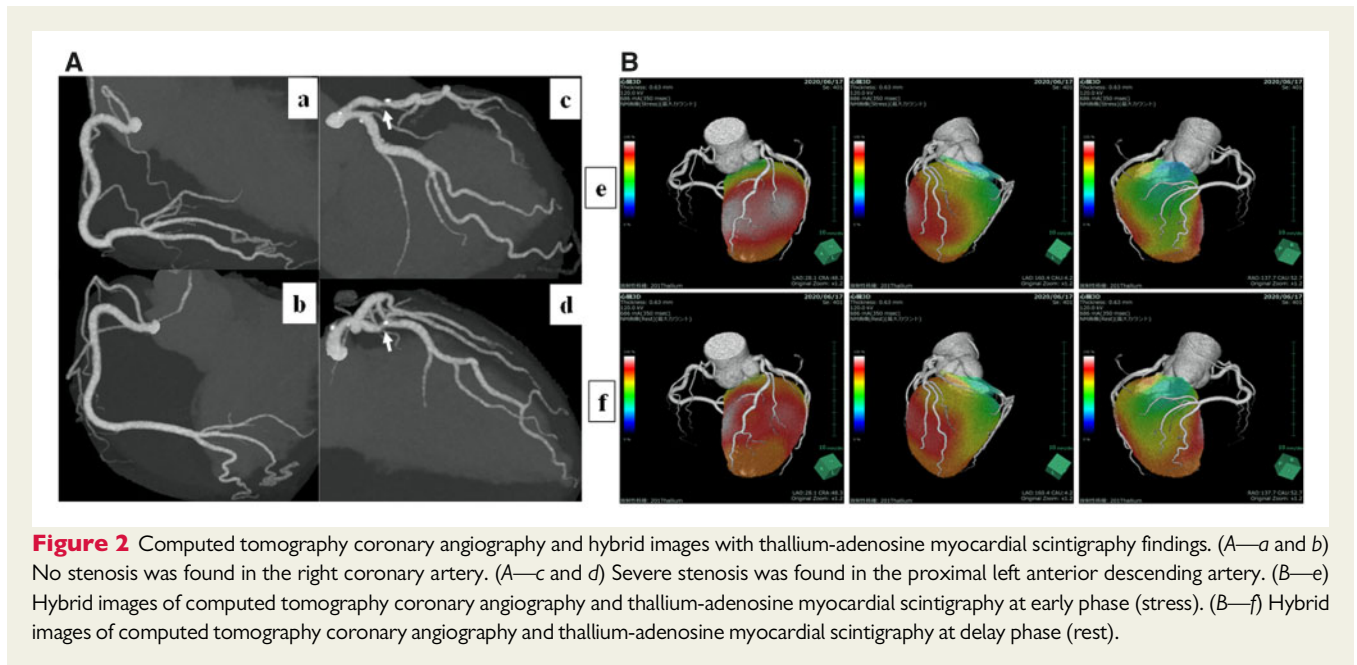


Figure 2 Computed tomography coronary angiography and hybrid images with thallium-adenosine myocardial scintigraphy findings. (A—a and b) No stenosis was found in the right coronary artery. (A—c and d) Severe stenosis was found in the proximal left anterior descending artery. (B—e) Hybrid images of computed tomography coronary angiography and thallium-adenosine myocardial scintigraphy at early phase (stress). (B—f) Hybrid images of computed tomography coronary angiography and thallium-adenosine myocardial scintigraphy at delay phase (rest).

Discussion

In this case report, we showed typical CSA with syncope. Intracoronary ER administration did not provoke spasm, but intracoronary injection of ACh documented typical diffuse spasm at the distal LAD artery. Because neither bradycardia nor cardiac arrest has occurred during administration of ACh for 30 s, we might be able to perform ACh tests without pacemakers in the LCA. After cardiologists observe a negative ER test when they suspect CSA, intracoronary administration of ACh

into the LCA without a pacemaker may be one option for pharmacological testing if neither bradycardia nor arrest is found.

According to previous reports, there were no differences regarding the incidence of provoked spasm in the same CSA patients between ACh and ER tests, as shown in [Table 1](#).^{10,11} We also reported the frequency of provoked spasms in the same 171 patients with ischaemic heart disease between ACh and ER testing.¹² ACh-inducible spasms are diffuse and distal, whereas ER-provoked spasms are proximal and focal.^{12,13} Because a single spasm provocation test has some

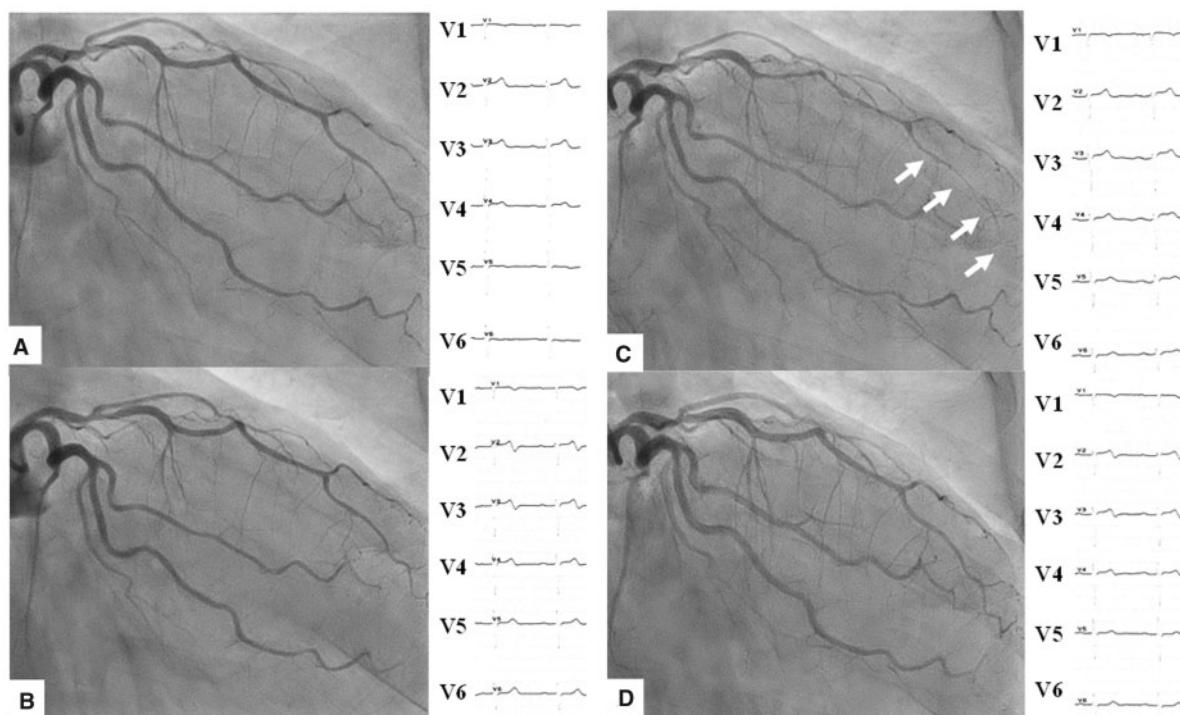


Figure 3 Ergonovine and acetylcholine testing in the left coronary artery. (A) Intracoronary injection of 64 μg ergonovine disclosed no spasm and no ischaemic electrocardiogram changes. (B) No provoked spasm or no ischaemic electrocardiogram changes were recognized after adding 40 μg ergonovine into the left coronary artery. (C) Diffuse spasm was recognized at the distal left anterior descending artery accompanied by typical chest pain and aura before syncope after the administration of 100 μg acetylcholine without a pacemaker. Slight ST elevation (0.5 mm) on V2–4 anterior leads was observed. (D) Proximal mild stenosis in the left anterior descending artery was found after the administration of nitroglycerine.

Table 1 Comparisons of acetylcholine and ergonovine spasm provocation tests in the same patients

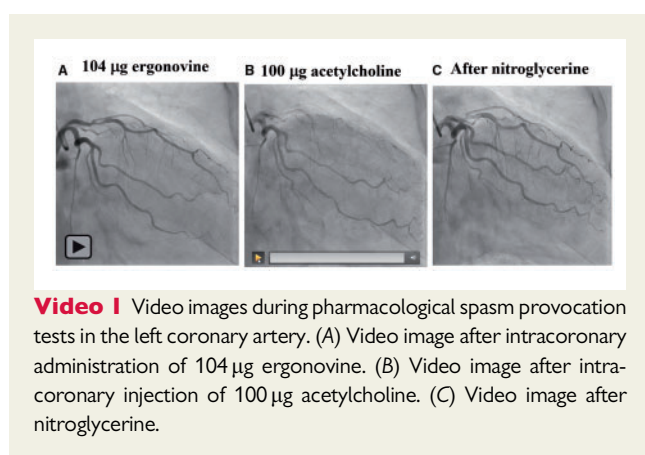
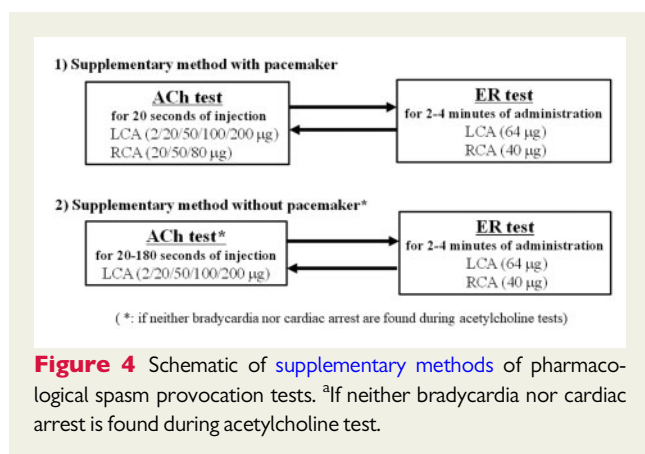
	Suzuki <i>et al.</i>	Kanazawa <i>et al.</i>	Suzuki <i>et al.</i> and Kanazawa <i>et al.</i>	Sueda <i>et al.</i>	Suzuki <i>et al.</i> and Kanazawa <i>et al.</i> and Sueda <i>et al.</i>
Diagnosis	CSA	CSA	CSA	IHD	CSA and IHD
Patient number	11	20	31	171	202
Male/female	9/2	15/5	24/7	106/65	130/72
Age (years)	54 \pm 9	57 \pm 10		62 \pm 10	
Procedures	ACh \rightarrow ER	ACh \rightarrow ER		ACh \rightarrow ER	
Dose of ACh (μg)	25/50/100	50/100		20/50/80/100	
Dose of ER (μg)	1/5/10/30	40		40/64	
Definition of positive spasm	>99%	>90%		>99%	
Positive spasm by ACh test	82% (9/11)	80% (16/20)	81% (25/31)	33% (56/171)	40% (81/202)
Positive spasm by ER test	100% (11/11)	65% (13/20)	77% (24/31)	32% (54/171)	39% (78/202)

ACh, acetylcholine; CSA, coronary spastic angina; ER, ergonovine; IHD, ischaemic heart disease.

limitations of clinical spasms in the cardiac catheterization laboratory, we recommend supplementary tests as shown in [Figure 4](#) and sequential spasm provocation tests whenever possible.¹⁴

The administration of 20 mg metoprolol before CTCAG may aggravate coronary artery vasomotor reactivity in this case. It may be better to select benzodiazepine calcium channel blockers, such as diltiazem hydrochloride or verapamil hydrochloride,

instead of beta-blockers when performing CTCAG in patients with resting angina.¹⁵ In this case, ischaemic electrocardiogram changes were recognized on V5, V6 leads during aura before syncope, whereas slight ST elevation (0.5 mm) on V2–V4 anterior leads was observed in ACh testing. Because we did not perform ACh tests in the RCA, we had no proof of ACh-inducible spasm in the RCA.



According to the JCS guidelines, pacemaker insertion is necessary for ACh testing. In our prior publication, we demonstrated that approximately 46% of patients had no back-up pacemaker support in the LCA ACh tests for 20 s of injection.¹⁶ We slowly injected ACh into the LCA at low doses of 20 µg and 50 µg for 30 s. Because no bradycardia or arrest was found, we administered 100 µg ACh into the LCA for 30 s. Diffuse distal spasm at the LAD artery accompanied by typical chest pain was observed in this case. We were able to diagnose this case as CSA. We did not perform the ACh test in the RCA. Intracoronary administration of ACh into the RCA for 20 s of injection had back-up support pacemaker rhythm in approximately 86% of patients.¹⁶ In the clinic, cardiologists may be able to select an intracoronary ACh test without a pacemaker in the LCA but not the RCA. However, when intracoronary injection of ACh reveals bradycardia or arrest, we should perform ACh tests after the insertion of the pacemaker. The invasive intracoronary ACh test is safe for documentation of coronary spasm in the clinic.

Conclusions

Different coronary responses between ACh and ER were revealed in this case. Because a single spasm provocation test has some limitations of clinical spasms, we recommend supplementary and sequential spasm

provocation tests whenever possible. After cardiologists observe a negative ER test when they suspect CSA, intracoronary administration of ACh into the LCA without a pacemaker may be one option for pharmacological testing if neither bradycardia nor arrest is found.

Lead author biography



Shozo Sueda have been interested in coronary artery spasm for more than 30 years. I have performed spasm provocation tests more than 3000 cases including 1800 acetylcholine testing and 1200 ergonovine tests. I have learned many things from these pharmacological spasm provocation tests. Japanese Circulation Society guideline and COVADIS group defined spasm provocation test as class I, while ACC/AHA guideline and

ESC guideline classified spasm provocation test as class IIb and class IIa, respectively. Spasm provocation test should be classified as class I in all over the world.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

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References

- Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj S. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the Management of Stable Coronary Artery Disease of the European Society of Cardiology [published correction appears in *Eur Heart J* 2014; 35: 2260-2261]. *Eur Heart J* 2013;34:2949-3003.
- Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey JD. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction:

- a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2013; 127: e863-e864]. *Circulation* 2012;**127**:e663–e828.
3. Beltrame JF, Crea F, Kaski JC, Ogawa H, Ong P, Sechtem U et al.; on behalf of the Coronary Vasomotion Disorders International Study Group (COVADIS). International standardization of diagnostic criteria for vasospastic angina. *Eur Heart J* 2017;**38**:2565–2568.
 4. JCS joint working group. Guidelines for diagnosis and treatment of patients with vasospastic angina (Coronary spastic angina) (JCS 2013). *Circ J* 2014;**78**:2779–2801.
 5. Sueda S, Miyoshi T, Sasaki Y, Sakaue T, Habara H, Kohno H. Gender differences in sensitivity of acetylcholine and ergonovine to coronary spasm provocation test. *Heart Vessels* 2016;**31**:322–329.
 6. Sueda S, Kohno H, Fukuda H, Ochi N, Kawada H, Hayashi Y et al. Clinical impact of selective spasm provocation tests: comparisons between acetylcholine and ergonovine in 1508 examinations. *Coron Artery Dis* 2004;**15**:491–497.
 7. Sato K, Kaikita K, Nakayama N, Horio E, Yoshimura H, Ono T et al. Coronary vasomotor response to intracoronary acetylcholine injection, clinical features, and long-term prognosis in 873 consecutive patients with coronary spasm: analysis of a single-center study over 20 years. *J Am Heart Assoc* 2013;**2**:e000227.
 8. Ong P, Athanasiadis A, Borgulya G, Mahrholdt H, Kaski JC, Sechtem U. High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries: the ACOVA study. *J Am Coll Cardiol* 2012;**59**:655–662.
 9. Cury RC, Abbara S, Achenbach S, Agatston A, Berman DS, Budoff MJ. CAD-RADS™: coronary artery disease—reporting and data system. An expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Radiology (ACR) and the North American Society for Cardiovascular Imaging (NASCI). Endorsed by the American College of Cardiology. *J Cardiovasc Comput Tomogr* 2016;**10**:269–281.
 10. Suzuki Y, Tokunaga S, Ikeguchi S, Miki S, Iwase T, Tomita T et al. Induction of coronary artery spasm by intracoronary acetylcholine: comparison with intracoronary ergonovine. *Am Heart J* 1992;**124**:39–47.
 11. Kanazawa K, Suematsu M, Ishida T, Hirata K, Kawashima S, Akita H et al. Disparity between serotonin- and acetylcholine-provoked coronary artery spasm. *Clin Cardiol* 1997;**20**:146–152.
 12. Sueda S, Kohno H, Fukuda H, Ochi N, Kawada H, Hayashi Y et al. Induction of coronary artery response by two pharmacological agents: comparison between intracoronary injection of acetylcholine and ergonovine. *Coron Artery Dis* 2003;**14**:451–457.
 13. Sueda S, Kohno H, Ochi T, Uraoka T, Tsunemitsu K. Overview of the pharmacological spasm provocation test: Comparisons between acetylcholine and ergonovine. *J Cardiol* 2017;**69**:57–65.
 14. Sueda S, Miyoshi T, Sasaki Y, Sakaue T, Habara H, Kohno H. Sequential spasm provocation tests might overcome a limitation of the standard spasm provocation tests. *Coron Artery Dis* 2015;**26**:490–494.
 15. Sueda S, Kohno H. Spontaneous coronary artery spasm detected by computed tomography coronary angiography: provoked spasm site similar to intracoronary injection of ergonovine but not acetylcholine. *J Cardiol Cases* 2019;**20**:209–212.
 16. Sueda S, Fujimoto K, Sasaki Y, Kohno H. Necessity of back-up pacemaker support during acetylcholine testing as a safe method. *Coron Artery Dis* 2020;**31**:197–198.